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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,808	09/16/2003	Sylvie Roux	03495.0174-02000	2497

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
04/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/662,808	ROUX ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,33 and 68-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32, 33 and 68-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the appeal brief filed on 2-8-08, PROSECUTION IS HEREBY REOPENED. New grounds of rejection set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632

Claims 32, 33 and 68-73 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 32, 33 and 68-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing the concentration of tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin (TTC) in neuromuscular junction (NMJ) by injecting brain derivated neurotrophic factor (BDNF), GDNF or neurotrophin (NT) 4 into Levator auris longus (LAL) muscle or gastrocnemius muscle of mice, does not reasonably provide enablement for a method of decreasing neuronal transport of tetanus toxin or TTC by administering tetanus toxin or TTC in combination with BDNF, GDNF or NT4 via various administration routes in vivo, or a method of modulating neuronal transport of tetanus toxin or TTC in vivo without administration of tetanus toxin or TTC. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 32, 33 and 68-73 are directed to a method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin comprising administering to the neuron a BDNF, a NT-4 or GDNF to modulate the neuronal transport of said tetanus toxin or fusion protein. Claim 33 specifies the BDNF, GDNF or NT-4 increases the internalization of the tetanus toxin or fusion protein at a neuromuscular junction. Claims 68-70 specify the tetanus toxin is administered with BDNF, NT-4 and GDNF, respectively. Claims 71-73 specify the fusion protein comprising TTC is administered with BDNF, NT-4 and GDNF, respectively.

The specification discloses that co-injection of GFP-TTC with either BDNF or NT-4 into Levator auris longus (LAL) muscle or gastrocnemius muscle of mice increases concentration of GFP-TTC at the neuromuscular junction as compared to control (e.g. p. 32-35, example 8-10) and localization of GFP-TTC at the NMJ is rapidly induced by neurotrophic factors such as BDNF, NT-4 and GDNF but not NGF, NT-3 and CNTF. As indicated in the instant invention, the term "modulate" encompasses the term "increase" and "decrease" (specification, [025]). The claims encompass both increase and decrease neuronal transport of tetanus toxin or TTC in vivo by using BDNF, GDNF or NT-4, however, the specification shows that BDNF, GDNF and NT-4 only "increases" the concentration of tetanus toxin or a fusion protein comprising TTC in

neuromuscular junction (NMJ). Therefore, the specification fails to provide enabling disclosure for "decreasing" the neuronal transport of tetanus toxin or TTC by using BDNF, GDNF, or NT-4 in vivo via various administration routes. The claims are not enabled for "decreasing" the neuronal transport of tetanus toxin or TTC by using BDNF, GDNF, or NT-4 in vitro or in vivo via various administration routes.

Claims 32 and 33 read on only administering BDNF, GDNF or NT-4 to the neuron but NO tetanus toxin or fusion protein comprising TTC is administered. The specification fails to provide adequate guidance and evidence for how to "modulate" neuronal transport of tetanus toxin or TTC without the presence of tetanus toxin or TTC. Absent specific guidance, one skilled in the art at the time of the invention would not know how to "modulate" neuronal transport of tetanus toxin or TTC without the presence of tetanus toxin or TTC at the target site.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 32, 33 and 68-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoop et al., 1996 (The Journal of Neuroscience, Vol. 16, No. 10, p. 3256-3264) in view of Miana-Mena et al., 2002 (PNAS, Vol. 99, No. 5, p. 3234-3239) and Poo, M-M., 2001 (Nature Review, Neuroscience, Vol. 2, p. 24-32).

Claims 32, 33 and 68-73 are directed to a method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin comprising administering to the neuron a BDNF, a NT-4 or GDNF to modulate the neuronal transport of said tetanus toxin or fusion protein. Claim 33 specifies the BDNF, GDNF or NT-4 increases the internalization of the tetanus toxin or fusion protein at a neuromuscular junction. Claims 68-70 specify the tetanus toxin is administered with BDNF, NT-4 and GDNF, respectively. Claims 71-73 specify the fusion protein comprising TTC is administered with BDNF, NT-4 and GDNF, respectively.

Stoop teaches extracellular application of brain-derived neurotrophic factor (BDNF) to developing neuromuscular junctions in Xenopus nerve-muscle cultures resulted in an increase in

the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and an increase in presynaptic cytosolic Ca2+. BDNF has potentiation effect on spontaneous transmitter release (e.g. abstract).

Stoop does not teach neurotrophin, such as BDNF, GDNF and NT-4, can stimulate neuronal transport of tetanus toxin or TTC.

Miana-Mena teaches injecting TTC-LacZ fusion protein intramuscularly and shows that intracellular and transneuronal traffics of the fusion protein on both sides of the synapse are strongly dependent on presynaptic neural cell activity. Miana-Mena suggests that "[s]uch fusion protein, sensitive to presynaptic neuronal activity, would be extremely useful to analyze morphological changes and plasticity at the NMJ" (e.g. abstract).

Poo teaches that "synaptic activity regulates the synthesis, secretion and action of neurotrophins, which can in turn induce immediate changes in synaptic efficacy and morphology" and "neurotrophins may participate in activity-dependent synaptic plasticity, linking synaptic activity with long-term functional and structural modification of synaptic connections" (e.g. abstract).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use BDNF, NT-4 or GDNF to modulate neuronal transport of tetanus toxin or TTC in neuromuscular junction because neurotrophin BDNF can increase the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and increase presynaptic cytosolic Ca2+ concentration, and Miana-Mena teaches that intracellular and transneuronal traffics of TTC-LacZ fusion protein strongly depend on presynaptic neural cell activity. One of ordinary skill in the art would find it obvious to use BDNF to modulate

neuronal transport of tetanus toxin or TTC because there is a correlation between increase in presynaptic neural cell activity and increase in intracellular and intraneuromal traffics of TTC-LacZ fusion protein. Since NT-4 and GDNF are well known neurotrophin in the art and Poo teaches that neurotrophins may participate in activity-dependent synaptic plasticity, linking synaptic activity with long-term functional and structural modification of synaptic connections, therefore, it would have been obvious for one of ordinary skill in the art to use NT-4 or GDNF to modulate neuronal traffic of TTC at neuromuscular junction.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to determine the intracellular and transneuronal traffics of the TTC-LacZ fusion protein on both sides of the synapse as taught by Miana-Mena with reasonable expectation of success.

Priority

The subject matter of the instant invention, i.e. a method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin by using BDNF, NT-4 or GDNF in vitro or in vivo, has not been disclosed by Application Nos. 09/816,467, 09/129,368, 60/055,615 and 60/065,236. Therefore, the claimed priorities of those applications set forth above are NOT granted. The effective filing date of the instant invention is the filing date of the instant application, i.e. 9-16-03.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

/Shin-Lin Chen/
Primary Examiner, Art Unit 1632